CLINICAL REVIEW

Application Type	NDA
Submission Number	[redacted]
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Letter Date	June, 12, 2006
Stamp Date	June 12, 2006
PDUFA Goal Date	December 10, 2007
Reviewer Name	Dragos Roman
Review Completion Date	December 3, 2007
Established Name	Testosterone gel 1 %
(Proposed) Trade Name	AndroGel
Therapeutic Class	Testosterone (androgen)
Applicant	Solvay Pharmaceuticals
Priority Designation	P
Formulation	Metered-dose pump (1.25 g per actuation) and individual packets (2.5 g and 5 g, respectively)
Dosing Regimen	Dosing Regimen 0.5 g, 1.5 g or 2.5 g daily

Indication	Delayed puberty
Intended Population	Hypogonadism (primary and secondary) and constitutional delay of growth and puberty

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

1.1.1 Hypogonadism indication: Non-approval

Given that the applicant has not proved convincingly that the proposed AndroGel dose of 0.5 g/day is an appropriate starting dose for testosterone replacement in children with pubertal delay secondary to primary or secondary hypogonadism, and taking into consideration that inappropriately high doses of testosterone carry an intrinsic risk of undue acceleration of bone age (and potential loss in linear growth potential), the currently proposed pediatric regimen of AndroGel should be not be approved. In order to gain approval for AndroGel in pediatric patients the applicant should select a lower dose (or lower doses) of AndroGel and characterize it (them) fully.

1.1.2 Constitutional delay of growth and puberty indication: Non-approval

This reviewer recommends against approving AndroGel for the treatment of constitutional delay of growth and puberty (CDGP) because the applicant has not established a safe and effective regimen for children with this CDGP[1]. In contrast to hypogonadism (a condition wherein testosterone treatment is replacement therapy and testosterone is titrated with the clear goal of reaching well characterized, Tanner stage-specific serum testosterone concentrations), testosterone treatment in CDGP is a transient pharmacological intervention aimed at "jumpstarting" puberty. Therefore, a safe and effective regimen in CDGP has to establish a dose, a duration of treatment, and a clearly defined clinical endpoint (none of which is demonstrated in this submission). In addition, since CDGP patients reach, albeit in a delayed fashion, normal height and sexual maturity, any safe and effective regimen should demonstrate that it does not affect negatively final height (or at least bone age advancement and/or predicted adult height).

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None at this point.

[1]It is important to recognize that only a subgroup of children with this normal variant of puberty is currently being treated; they are children who exhibit psychological adverse effects related to being behind their peers in somatic development.

1.2.2 Required Phase 4 Commitments

None at this point.

1.2.3 Other Phase 4 Requests

None at this point.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

AndroGel® is 1 % testosterone manufactured as a hydroalcoholic gel for cutaneous administration. Approved in 2000 under NDA 21-015 for the treatment of primary and secondary hypogonadism in adults, AndroGel is to be administered once daily in doses of 5 g, 7.5 g, or 10 g (which contain 50 mg, 75 mg, and 100 mf of testosterone, respectively) and is supplied as metered-dose pump[2] and individual unit-dose packets[3].

On June 21, 2002 the Division of Endocrinology and Metabolism Products (DMEP) issued a
Written Request (WR) to Unimed Pharmaceuticals Inc. for the indication of delayed puberty in boys. The final version of the WR (dated May 24, 2007) requested the following two studies:

- Study 1: a pharmacokinetic (PK) study of testosterone 1% gel in boys with delayed puberty.
- Study 2: a dose titration and safety study of testosterone 1% gel in boys with delayed puberty.

In response to the WR, the applicant conducted studies UMD-01-080 and UMD-01-090.

Study UMD-01-080 (Study 1 of the WR) was a multicenter, open-label, escalating-dose study conducted in 17 boys with delayed puberty due to hypogonadism or constitutional delay of growth and puberty[4]. The study evaluated the pharmacokinetic profile of three proposed pediatric AndroGel doses: 0.5 g, 1.5 g, and 2.5 g (containing 5 mg, 15 mg, and 25 mg of testosterone, respectively).

Study UMD-01-090 (Study 2 of the WR) was a single-arm, open-label, multicenter, 6-month, observational study of AndroGel treatment that was conducted in 86 males aged

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[2] A metered-dose pump contains 75 g of of AndroGel (or 60 metered 1.25 g doses).
[3] Individual packets are supplied as 2.5 g and 5 g packets, respectively.
[4] Of the 17 patients enrolled, 6 patients (35.3%) had a diagnosis of primary hypogonadism, 7 patients (41.2%) had a diagnosis of secondary hypogonadism and 4 patients (23.5%) had a diagnosis of CDGP. Approximately two-thirds of all patients were naive to androgen therapy prior to entering the study (11 patients or 64.7%). Patients received a single AndroGel dose for 4 days prior to PK evaluation; after an approximately 14 day washout the next ascending dose was applied.

13-18 years with a diagnosis of delayed puberty due to primary or secondary hypogonadism, or CDGP[5]. Study treatment began with a 3-week titration period aimed at bringing serum testosterone concentrations in a range deemed appropriate for each patient's Tanner stage[6], followed by a maintenance phase wherein the AndroGel dose was kept more or less constant. The daily AndroGel doses were the same three doses that were evaluated pharmacokinetically in Study 1 (i.e. 0.5 g, 1.5 g, and 2.5 g). The starting dose was 0.5 g daily; dose escalation was based on measured serum testosterone concentrations at steady state. The goal of this study, as stated in the WR, was "to establish a dose regimen that can be safely used for initiating or for progressing puberty". To this end, this study was not designed to evaluate the efficacy of AndroGel whose active ingredient (testosterone) is well characterized and understood in both physiologic and non-physiologic states, but rather to evaluate a starting dose of AndroGel in adolescents, gather information on serum testosterone levels for the pediatric dose regimens proposed, and assess safety (in particular the advancement of bone age relative to that of chronological age).

1.3.2 Efficacy

As mentioned above, Study UMD-01-090 was not an efficacy study (the WR defined it as a"dose titration and safety study") and did not include a control group. Consequently the efficacy assessments collected in Study UMD-01-090 provided very limited information. In addition, even the efficacy analyses performed were largely noninformative due to the heterogeneity[7] of the patient population enrolled in the study and to multiple protocol violations (for instance 19/86 or 22.1% patients were enrolled despite not meeting the inclusion criteria for testosterone level and/or testicular volume).

Study UMD-01-090, however, collected extensive dose-exposure data (specifically, serum testosterone levels in over 70 patients for up to 6 months over the whole range of doses administered), thus expanding considerably the information provided in the pharmacokinetic Study UMD-01-080. The significance of these data is discussed in the Dosage and Administration Section.

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[5] Of the 86 patients enrolled, 59 (69%) had a diagnosis of primary or secondary hypogonadism and 27 (31%) had a diagnosis of CDGP. Of the hypogonadal patients 61% had primary hypogonadism and 39% had secondary hypogonadism; 49% of the hypogonadal patients were naïve to testosterone treatment.

[6] The initial titration goal was 100-200 ng/dL. Following an amendment (Amendment 6) this goal was abandoned.

[7] Part of the basis for heterogeneity was that the study included both testosterone-naïve and non-naïve patients. More importantly, however, many patients were already in puberty at baseline: 79 % of hypogonadal patients and 52 % of CDGP patients were ≥ Tanner II and, across diagnostic groups, 19 patients or 22% were already Tanner IV or V (prepubertal and pubertal patients have different initial titration goals). In addition, since some hypogonadal and CDGP patients had endogenous testosterone production (as indicated by high screening and/or baseline total testosterone serum concentrations), it is impossible to differentiate the clinical effects of AndroGel from those due to the endogenous testosterone. Finally, unusually high testosterone levels at baseline observed in some patients may have been due to incomplete washout of prior testosterone treatment in non-naïve patients; as this was an uncontrolled study, reliable baseline information is critical for drawing efficacy conclusions.

1.3.3 Safety

The safety information collected from 86 patients treated for 6 months with AndroGel during trial UMD-01-090 does not identify any new safety signals specific to the pediatric population. This should not be surprising since the active ingredient in AndroGel is testosterone, a compound well characterized in both adults and adolescents. In addition, it should be recognized that, at least for hypogonadal patients, testosterone treatment with AndroGel is not pharmacological but rather replacement therapy aimed at reaching serum testosterone levels appropriate for various normal stages of puberty.

There were no patient deaths in either study. There were four serious adverse events, all in Study UMD-01-090[8]. Only one of them (slipped femoral epiphysis head) was considered possibly related to study medication. Only one patient discontinued the trial for an adverse event (depression).

There was no specific pattern of treatment-emergent adverse events in any of the two studies. The adverse events encountered were mostly manifestations of childhood illnesses. Most adverse events were mild in intensity, some moderate and very few were severe[9]. Although as many as 48 patients (55.8%) experienced a TEAE that was judged "related" to study medication, acne is the only adverse event that can be mechanistically attributed with a reasonable degree of certainty to the study drug. Firm conclusions are difficult to draw due to the absence of a control group.

Standard clinical laboratory and vital signs evaluations did not show any clinically meaningful changes on AndroGel treatment.

1.3.4 Dosing Regimen and Administration

The studies submitted with this NDA evaluate three pediatric AndroGel doses: 0.5 g/day, 1.5 g/day, and 2.5 g/day, respectively. These three doses were selected with the goal of providing serum testosterone concentrations that cover the whole range of testosterone values expected during adolescence. Since serum testosterone concentrations are not uniform throughout puberty but rather increase gradually as the hypothalamic-pituitary-gonadal axis matures, AndroGel treatment is to be started with the low dose (0.5 g/day) and escalated as needed to higher doses (1 g/day and 2.5 g/day) toward adult doses at the end of puberty (5 g/day through 10 g/day). Thus, it is reasonable to assume that, once a safe starting dose of AndroGel is established, given the availability of intermediary pediatric doses, as well as the currently approved adult doses, testosterone titration can be achieved safely with periodic monitoring of serum testosterone, bone age advancement, Tanner stage progression, and growth velocity[10]. It is for these reasons that this review

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[8] Severe adjustment disorder with depressed mood, appendicitis, slipped femoral epiphysis head, and severe depression.

[9] All severe adverse events were in study UMD-01-090 and all were captured as serious adverse events, described above.

[10] Generally speaking, a starting dose of AndroGel is expected to be low enough to generate serum

places particular emphasis on the starting AndroGel dose of 0.5 g/day. It should be emphasized that the 0.5 g dose was in fact the most widely used AndroGel dose in the trial, with approximately 30-40 % of patients receiving it at any given time.

Regretfully, the applicant has not proved convincingly that the proposed starting AndroGel dose of 0.5 g/day is low enough to safely initiate testosterone replacement in children. Although the baseline-subtracted mean serum testosterone concentration obtained with the 0.5 g of AndroGel was in general acceptable (e.g. approximately 80 ng/dL, consistent with a Tanner II serum testosterone level), the range of individual values included a significant proportion of patients with relatively high testosterone levels (some close to, or even in the adult range). In order to assess critically this observation this reviewer used a baseline subtracted testosterone value in excess of 200 ng/dl as an indicator of high testosterone levels. This is a non-conservative "threshold" value and was selected for the following reasons: 1) it represents a testosterone concentration at the upper end for that seen in Tanner II patients (or even above the Tanner II range in some references), 2) it is very close to the mean serum testosterone concentrations for Tanner III patients, and 3) it is close to the lower end of Tanner V and adult levels. It is worth mentioning that the 200 ng/dL was also the upper limit of the AndroGel titration goal for the better part of Study UMD-01-090 (testosterone naïve patients were titrated, at least initially, to a range of 100-200 ng/dL).

Four sets of observations indicate that serum testosterone concentrations over 200 ng/dL are not rare occurrences in association with the 0.5 g AndroGel dose:

1) In study UMD-01-080 the baseline subtracted serum testosterone concentration at steady state exceeded 200 mg/dl in 2/17 (11.7%) patients.[11]
2) In study UMD-01-090 between 10% and 12.2% of patients (depending on the type of analysis conducted) had baseline subtracted serum testosterone values upward of 200 ng/dL at Week 1, the first timepoint on trial. The Week 1 timepoint is particularly informative because all patients were to have received the starting dose of 0.5 g per day up to this timepoint[12] and the measured testosterone levels were at steady state. Thus, this timepoint provides the largest set of individual testosterone measurements obtained with the 0.5 g AndroGel dose and the serum testosterone levels measured at this time should give the best approximation of the range of levels expected with this dose.
3) In hypogonadal patients (a subgroup of patients with relatively constant testosterone background) testosterone levels > 200 mg/dl were not uncommon on the 0.5 g/day dose (as low as 8.3% and as high as 44% or above)[13].

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testosterone levels that do not exceed those associated with the early stages of puberty (e.g. Tanner II) and provide reassurance that it does not accelerate unduly bone age at least short-term (otherwise it would raise the concern of loss in final height).

[11] Patient 2001 had values of [redacted] ng/dL (along with values of [redacted] ng/dL, respectively) in a 24 hour profile. Patients 2002 had a single value of [redacted] ng/dL out of 6 values in a 24-hour profile.

[12] In fact, according to Table 10.2.10 (A), 75/76 patients received the 0.5 g AndroGel dose at Week 1.

[13] 7/52 or 13.5% patients at Week 1; 4/25 or 16% patients at Week 2; 3/4 (75%) patients at Week 3; 4/19 (21%) patients at Month 1; 8/18 (44%) patients at Month 2; 2/15 (13.3%) patients at Month 3; 1/12 (8.3%) patients at Month 4; and 5/13 (38.4%) patients at Month 6. Some of these patients (as well as other patients

4) In the 29 patients who used the 0.5 g daily AndroGel dose at all times throughout the trial[14], serum testosterone values greater than 200 ng/dL were observed relatively frequently; these patients (and in particular the ones with hypogonadism) are also very informative because they represent patients who either could not be titrated above the starting dose or who did not need to be titrated higher in the judgment of the investigator.

The relatively high percentage of observations of baseline-subtracted serum testosterone concentrations above 200 ng/dL observed with the starting AndroGel dose of 0.5 g/day raises the question of whether this dose is indeed low enough to safely initiate testosterone replacement. Unfortunately, the data collected on bone age advancement during trial UMD-01-090 and presented in this submission are not robust enough to provide reassurance that the 0.5 g dose does not accelerate bone age maturation: approximately 10% of patients had missing or uninterpretable bone age films, some had biologically implausible observations (11 patients had a reduction of bone age at the end of the trial relative to baseline), and the remaining dataset is too small to allow for meaningful conclusions[15].

In addition to the above listed observations, scatter plots of individual serum concentrations of total testosterone achieved with each specific dose indicate that the 0.5 g daily AndroGel dose was associated, not infrequently, with absolute serum testosterone concentrations in the adult range of 300-1,000 ng/dl at each of the timepoints evaluated in the trial. This is the most direct evidence that the AndroGel dose of 0.5 g is associated with exceedingly high serum testosterone concentrations and that it fails to meet the expectations of a starting dose.

In conclusion, from a clinical perspective, the results of Study UMD-01-090 do not provide convincing evidence that AndroGel 0.5 g is an appropriate starting dose for the treatment of delayed puberty. The execution of the study (inclusion of a very heterogeneous patient population, multiple protocol violations, and shortcomings in the quality of bone age data) complicates further the interpretation of an already limited dataset. Finally, and importantly, a routine, audit of the testosterone data collected in Study UMD-01-090, concluded that there were "significant deficiencies that impact[ed] the integrity of the data generated by [redacted] is the clinical laboratory where the testosterone data were centrally analyzed); these deficiencies concerned both

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in the study) received AndroGel for part of the trial via the wrong pump head (the '[redacted] pump head"), which delivered a dose approximately 20% lower than planned (i.e. 0.4 g instead of 0.5 g). This implies that even higher serum testosterone levels may be anticipated with a 0.5 g dose.

[14] 14 patients with hypogonadism and 15 patients with CDGP.

[15] The limitations of the interpretability of the bone age dataset are illustrated by the following facts: of the 27 patients who received the "low" cumulative AndroGel dose (roughly equivalent to the 0.5 g/day AndroGel dose) only 12 patients had both baseline and end-of-trial bone age information. Although the mean values for bone age advancement were similar to those for the chronological age advancement, a look at individual values indicate that 3 patients (25%) had bone age changes of one year for a chronological period of approximately 6 months.

the validation of the assay (accuracy, precision, linearity) and the analytical runs (for a detailed description of these deficiencies, refer to the clinical pharmacology review) [16].

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

1.3.5 Special Populations

No studies were conducted in patients with hepatic or renal failure.

[16] In addition, since Study UMD-01-080, although not formally evaluated by DSI, utilized the same testosterone assay methods used in Study UMD-01-090, this calls into question the reliability of the data collected in Study UMD-01-080as well.

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